LDK378 Compassionate Use for Treating Carcinomatous Meningitis in an ALK Translocated Non–Small-Cell Lung Cancer

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A 42-year-old woman, never smoker, complaining of chronic cough, underwent computed tomography that depicted a right lower lung mass and subcarinal lymphadenopathy. Disease was classified as stage IIIA lung adenocarcinoma (cT3N2M0), without an EGFR or KRAS mutation. After neo-adjuvant chemotherapy with cisplatin and gemcitabine, the patient underwent surgery comprising a right pneumonectomy and a lymph node dissection. One year and a half later, she was diagnosed with liver metastasis. The patient was treated with carboplatin, pemetrexed, and bevacizumab, achieving a stable disease for 9 months. Fluorescence in situ hybridization was performed, which revealed anaplastic lymphoma kinase (*ALK*) gene rearrangement. Crizotinib (ALK inhibitor) was started at disease progression. Tolerance was good and a partial response of hepatic lesions was observed. After 38 cycles of crizotinib (114 weeks on therapy), because the patient complained dizziness, full radiological screening showed stable liver lesions but brain magnetic resonance imaging revealed an appearance of carcinomatous meningitis associated with brain metastases. Lumbar punctions could not be performed because the patient refused. LDK378 was obtained for compassionate use and was started at a dose of 750 mg once daily. The treatment was well tolerated apart from nausea grade 2, thus the dose was reduced to 600 mg at day 60. The patient described rapid attenuation of dizziness. After 5 weeks of treatment, magnetic resonance imaging confirmed treatment efficacy with a decrease in brain lesions of 26% and in meningeal contrast (Fig. 1), that is still maintained after 5 and a half months.

DISCUSSION

ALK gene rearrangements occur in 3–7% of non–small-cell lung cancer (NSCLC) and are more prevalent in nonsmokers, younger patients, and adenocarcinomas.[1] Since August 2011, patients with ALK-rearranged NSCLC can be treated with crizotinib. Crizotinib is a potent, small molecule oral inhibitor of ALK, which has shown efficacy in ALK-rearranged NSCLC with an overall response rate (ORR) of 60.8% and a median progression-free survival duration of 9.7 months.[2] ORR to crizotinib is only 25% in brain metastasis.[3] The central nervous system (CNS) remains the dominant site of acquired resistance on therapy for ALK patients with or without brain metastasis. LDK378 (Novartis) is a new potent and selective oral ALK inhibitor. Tumor regression has been observed in ALK-positive NSCLC xenografts and even in crizotinib-resistant models. A phase I/II study evaluating LDK378 has shown promising results, with an ORR of 57% in crizotinib-treated patients, an ORR of 60% in crizotinib-naive patients, and a median progression-free survival duration of 8.6 months.[4] Moreover, LDK378 seems to have an

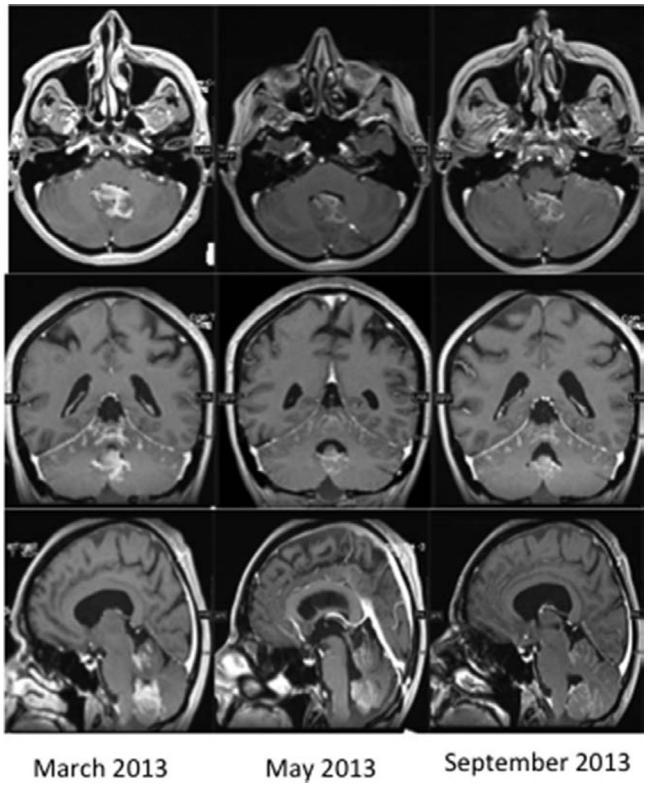

FIGURE 1. Brain radiological evaluating during LDK378 treatment.

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activity in the CNS, with a partial response on a brain metastase after 6 weeks of LDK378.[4] Then LDK378 is well tolerated with grade 1–2 nausea, diarrhea, vomiting, and fatigue as the common adverse events most described, as in our patient. Carcinomatous meningitis portends poor prognosis, with a median survival time after diagnosis of approximately 6–9 weeks. Currently, our patient is alive 6 months since the diagnosis with improvement of symptoms and radiological evidence of stable disease. Moreover, another highly selective ALK inhibitor, Alectinib (Roche), has been reported to be active in Crizotinib-resistant carcinomatous meningitis in a patient included in a phase I study.[5] Thus, second generation ALK inhibitors such as LDK378 seem to be highly efficient in ALK-positive NSCLC and more against CNS lesions.

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